REVIEW ARTICLE

Drugs 2001; 61 (15): 2163-2175
0012-6667/01/0015-2163/$27.50/0

© Adis International Limited. All rights reserved.

Interactions Between Herbal Medicines and Prescribed Drugs

A Systematic Review

Angelo A. Izzo[1] and *Edzard Ernst*[2]

1 Department of Experimental Pharmacology, University of Naples 'Federico II', Naples, Italy
2 Department of Complementary Medicine, School of Postgraduate Medicine and Health Sciences, University of Exeter, Exeter, United Kingdom

Contents

Abstract

Despite the widespread use of herbal medicines, documented herb-drug interactions are sparse. We have reviewed the literature to determine the possible interactions between the seven top-selling herbal medicines (ginkgo, St John's wort, ginseng, garlic, echinacea, saw palmetto and kava) and prescribed drugs. Literature searches were performed using the following databases: Medline (via Pubmed), Cochrane Library, Embase and phytobase (all from their inception to July 2000). All data relating to herb-drug interactions were included regardless of whether they were based on case reports, case series, clinical trials or other types of investigation in humans. *In vitro* experiments were excluded. Data were extracted by the first author and validated by the second author. 41 case reports or case series and 17 clinical trials were identified.

The results indicate that St John's wort (*Hypericum perforatum*) lowers blood concentrations of cyclosporin, amitriptyline, digoxin, indinavir, warfarin, phenprocoumon and theophylline; furthermore it causes intermenstrual bleeding, delirium or mild serotonin syndrome, respectively, when used concomitantly with oral contraceptives (ethinylestradiol/desogestrel), loperamide or selective serotonin-reuptake inhibitors (sertaline, paroxetine, nefazodone). Ginkgo (*Ginkgo*

biloba) interactions include bleeding when combined with warfarin, raised blood pressure when combined with a thiazide diuretic and coma when combined with trazodone. Ginseng (*Panax ginseng*) lowers blood concentrations of alcohol and warfarin, and induces mania if used concomitantly with phenelzine. Garlic (*Allium sativum*) changes pharmacokinetic variables of paracetamol, decreases blood concentrations of warfarin and produces hypoglycaemia when taken with chlorpropamide. Kava (*Piper methysticum*) increases 'off' periods in Parkinson patients taking levodopa and can cause a semicomatose state when given concomitantly with alprazolam. No interactions were found for echinacea (*Echinacea angustifolia, E. purpurea, E. pallida*) and saw palmetto (*Serenoa repens*).

In conclusion, interactions between herbal medicines and synthetic drugs exist and can have serious clinical consequences. Healthcare professionals should ask their patients about the use of herbal products and consider the possibility of herb-drug interactions.

Herbal medicines have become a popular option in healthcare. The seven best-selling herbal medicines in 1998 were ginkgo (retail sales in mainstream US market = $US150 million; percent increase compared with previous year = 67%), St John's wort ($US140 million; 190%), ginseng ($US96 million; 11%), garlic ($US84 million; 17%), echinacea ($US70 million; 42%), saw palmetto ($US32 million; 74%), and kava ($US17 million; 462%).[1] The data are even more impressive for Europe; for instance, the global market for all herbal and homeopathic remedies amounted to $US4.0 billion in North America and $US6.7 billion in Europe.[2] There is growing evidence for the efficacy of these herbal medicines.[3,4] However, safety issues associated with these treatments remain under-researched.[5] The fact that herbal medicines are associated with adverse events is widely appreciated.[2,4] Another area destined to gain importance is that of herb-drug interactions.[6]

All herbal medicines are mixtures of more than one active ingredient. In many cases it is uncertain which or how many constituents are pharmacologically important. On one hand, the multitude of active ingredients obviously increases the likelihood of interactions. On the other hand, this multitude combined with the fact that herbal medicines are of variable and often undefined composition renders any analysis of interactions a complex and difficult task. Because users of herbal medicines tend to have chronic conditions for which they often take prescribed drugs concomitantly, interactions are likely.[7] Thus, a review of this area is timely and relevant.

The aim of this article is to systematically review the existing clinical data on suspected interactions between the above-named herbal medicines and conventional drugs.

1. Systematic Review

1.1 Methods

Electronic literature searches were made using the following databases: Medline (via PubMed), Embase, Cochrane Library (2000 issue 2) and phytobase (all from their inception to July 2000). The search terms were the seven selected medicinal plants (English and German common names as well as botanical denominations) in combination with the terms 'drug interaction', 'adverse-effects', 'side effects', 'adverse drug reaction', 'safety', and 'toxicity'. Our search included alcohol (ethanol), as it can have therapeutic uses (i.e. treatment of poisoning by methanol).[8] Recent books[9-11] and articles[12-18] on herb-drug interactions or herbalism,[19-23] and recent reviews of the seven selected medicinal plants[24-30] were also searched for further relevant information. Additional publications were identified by checking all reference lists and by searching our files. Ten major manufacturers of herbal products, eight experts and 24 organisations related to medical herbalism were also contacted

© Adis International Limited. All rights reserved.

and asked for any information held on herb-drug interactions. No language restrictions were imposed.

All clinical reports on interactions were read and relevant data were extracted by the first author into predefined tables and validated by the second author. *In vitro* experiments were usually excluded.

1.2 Results

Forty one case reports or case series in 23 publications[31-53] and 17 clinical trials[54-70] were located. Key data from these publications are summarised in table I (case reports and case series) and table II (clinical trials). Obviously case reports have to be interpreted with great caution, as causality is not usually established beyond reasonable doubt.

2. Discussion

2.1 Garlic

Garlic (*Allium sativum*) is being promoted to lower cholesterol and blood pressure, delay atherosclerotic processes and improve circulation.[22] It has complex cardiovascular effects including antiplatelet activity.[24] Two case reports suggested that concomitant use of warfarin and garlic was followed by an increase in INR (international normalised ratio).[32] Other case reports highlighted its potential for increasing the risk of postoperative bleeding.[71,72] Animal[73] and clinical studies[74] imply hypoglycaemic effects, which could explain the fall in glucose levels in a Pakistani woman taking chlorpropamide and a curry containing garlic and karela (*Momordica charintia*).[31] A clinical trial[54] suggested that garlic changes some pharmacokinetic variables of paracetamol (acetaminophen) after 1 to 3 months' treatment. The precise mechanism of this interaction is presently not known.

2.2 Ginkgo

Ginkgo (*Ginkgo biloba*) is used mainly for memory loss, Alzheimer's disease and circulatory disorders.[25] Its constituents (ginkgolides, bilobalides and others) have antiplatelet activity and are platelet activating factor receptor antagonists.[25] Two case reports demonstrate that patients taking warfarin[33] or aspirin[36] have experienced severe spontaneous bleeding after self-prescribing ginkgo at recommended doses. Spontaneous bilateral subdural haematomas associated with long-term ginkgo ingestion have been reported.[75] The patient had already been prescribed paracetamol and a very brief trial of ergotamine/caffeine. It is unlikely that the adverse effect was due to the concomitant use of paracetamol (or ergotamine/caffeine) as the patient had a headache before taking these drugs; moreover, these prescribed drugs do not possess antiplatelet or anticoagulant activity.

Gingko is also a peripheral vasodilator.[25] Surprisingly, an elderly patient was found to have a further increase in blood pressure after taking ginko while receiving a thiazide diuretic (not specified in the original paper) for hypertension.[34] There is no rational pharmacological mechanism to explain this unusual interaction.

A patient with Alzheimer's disease fell into a coma after taking a combination of trazodone and ginkgo.[35] Ginkgo flavonoids increase the production of 1-(m-chlorophenyl) piperazine (mCPP), an active metabolite of trazodone, which releases γ-aminobutyric acid (GABA) through an agonistic action on presynaptic serotonin 5-HT_2 and α_2-adrenergic receptors located on GABAergic nerve terminals. In addition, flavonoids induce a further enhancement of GABAergic activity by acting on benzodiazepine binding sites. Consistent with this hypothesis, flavonoids have been shown to act as a partial agonist on benzodiazepine binding sites[76] and they also increase the activity of cytochrome P450 (CYP)3A4,[77] which metabolised trazodone to mCPP.

Ginkgo did not modify hormonal plasma levels (follicle-stimulating hormone, luteinising hormone, thyroid-stimulating hormone and prolactin) after stimulation tests with luteinising hormone-releasing hormone and thyrotropin-releasing hormone,[56] nor did it modify antipyrine (a substrate probe to study microsomal enzyme induction) half-

© Adis International Limited. All rights reserved.

Table I. Case reports and case series of possible interactions between herbal medicines and prescribed drugs

Herbal medicine dosage/duration	Sex (M/F)/age	Diagnosis	Prescribed drug dosage/duration	Concomitant drugs	Clinical result of interaction	Possible mechanism
Garlic[31] the patient used a curry containing garlic and karela	F/40y	Diabetes mellitus	Chlorpropamide[b]	None	Hypoglycaemia	Additive effect on glucose levels (garlic has antidiabetic activity)
Garlic[b][32]	2 pts[a]	None reported	Warfarin[b]	None mentioned	Increased INR; increase in clotting time	Additive effect on coagulation mechanisms (garlic has antiplatelet activity)
Ginkgo[33] (concentrated 50:1 extract) 40mg bid for 1wk	M/70y	Coronary-artery bypass	Aspirin 325 mg/d for 3y	None	Spontaneous hyphaema	Additive inhibition on platelet aggregation (ginkgo has antiplatelet activity)
Ginkgo[34] 1wk[b]	F/elderly[a]	Hypertension	Thiazide diuretic 1wk[b]	None mentioned	Increase in blood pressure	Not known
Ginkgo[35] (EGb716) 80mg bid for 3d	F/80y	Alzheimer's disease	Trazodone 20mg bid for 3d	Bromazepam, donapezil, Vitamin E, (in the past 3mo, but not concomitantly with ginkgo)	Coma (Glasgow coma scale 6/15)	Possible increase of GABAergic activity by ginkgo flavonoids
Ginkgo[36] 2mo[b]	F/78y	Coronary artery bypass and progressive dementia	Warfarin 5y[b]	None mentioned	Intracerebral hemorrhage	Additive effect on coagulation mechanisms (ginkgo has antiplatelet activity)
Ginseng[37] ginseng tea	F/64y	Depression	Phenelzine 45-60 mg/d[b]	None mentioned	Insomnia, headache, tremulousness	Increased cAMP levels by ginsenosides
Ginseng[b][38]	F/42y	Depression	Phenelzine 45mg/d	Bee pollen, triazolam, lorazepam	Maniac symptoms (irritability, hallucinations)	Increased cAMP levels by ginsenosides
Ginseng[39] (Ginsana®)[c] 3 capsules tid for 2 wks	M/47y	Heart valve replacement	Warfarin 5 mg/d for 5y; 7.5mg each Tuesday	Diltiazem, nitroglycerin, salsalate	Decreased INR (from about 3.3 to 1.5)	Not known
Kava[40] 3d[b]	M/54y	None reported	Alprazolam[b]	Cimetidine, terazosin	Lethargic and disoriented state	Additive effect on GABA receptors and release
Kava[41] (Kavasporal®)[c] 150mg bid for 10d	F/76y	Parkinson's disease	Levodopa 500 mg/d for 8y	Benserazide	Increase in the duration and number of 'off' periods	Dopamine antagonism
St John's wort[42] 300mg bid[b]	F/61y	Heart transplant	Cyclosporin[b]	None mentioned	Lowering of blood cyclosporin levels; rejection episode	Hepatic enzyme induction
St John's wort[42] 300mg tid[b]	F/54y	Lung fibrosis	Cyclosporin[b]	Prednisolone	Lowering of blood cyclosporin levels	Hepatic enzyme induction

© Adis International Limited. All rights reserved.

St John's wort[b][43]	30 patients[a]	Kidney transplant	Cyclosporin[b]	Other unreported drugs	Lowering of blood cyclosporin levels (47%)	Hepatic enzyme induction
St John's wort[b][44]	10 patients[a]	Liver transplant	Cyclosporin[b]	None mentioned	Lowering of blood cyclosporin levels (49%); rejection episode in 1 pt	Hepatic enzyme induction
St John's wort[45] 300 to 900mg daily (or St John's wort tea)[b]	5 patients[a]	Kidney transplant	Cyclosporin[b]	None mentioned	Lowering of blood cyclosporin levels	Hepatic enzyme induction
St John's wort[b][46]	F/mid-twenties	None reported	Cyclosporin[b]	None mentioned	Lowering of blood cyclosporin levels (75%)	Hepatic enzyme induction
St John's wort[47] (LI 160) 300mg tid for 3 wks	61y[a]	Heart transplant, mild depression	Cyclosporin 125mg bid for 11mo	Azathioprine, corticosteroids	Lowering of plasma cyclosporin levels to 95 g/L; rejection episodes	Hepatic enzyme induction
St John's wort[47] (LI160) 300mg tid for 3 wks	63y[a]	Heart transplant	Cyclosporin 125mg bid for 20mo	Azathioprine, corticosteroids	Lowering of blood cyclosporin levels to 87 g/L; rejection episode	Hepatic enzyme induction
St John's wort[b][48]	F/39y	Depression and migraine	Loperamide[b]	Valerian	Brief episode of acute delirium (disoriented, agitated, confused state)	Potentiation of MAO inhibition
St John's wort[b][49]	F[a]	None reported	Oral contraceptive[b]	None mentioned	Changed menstrual bleeding	Hepatic enzyme induction
St John's wort[b][49]	8 F 23-31y	None reported	Oral contraceptive long-term[b]	None mentioned	Intermenstrual bleeding	Hepatic enzyme induction
St John's wort[b][42]	F[a]	None reported	Oral contraceptive[b] ethinylestradiol 0.03mg/desogestrel 0.15mg	None mentioned	Intermenstrual (breakthrough) bleeding	Hepatic enzyme induction
St John's wort[b][42]	F[a]	None reported	Oral contraceptive[b] ethinylestradiol 0.02 mg/desogestrel 0.15mg	None mentioned	Intermenstrual (breakthrough) bleeding	Hepatic enzyme induction
St John's wort[b][42]	F/44y	No pathology reported	Oral contraceptive[b] ethinylestradiol 0.03g/desogestrel 0.15mg	None mentioned	Intermenstrual (breakthrough) bleeding	Hepatic enzyme induction
St John's wort[50] 300mg tid for 3d	F/84y	Depression and anxiety	Nefazodone 100mg bid[b]	None	Nausea, vomiting, headache	Synergistic serotonin uptake inhibition
St John's wort[b][50]	F/78y	Depression	Sertraline 50 mg/d[b]	Calcium carbonate and conjugated estrogens	Dizziness, nausea, vomiting, headache	Synergistic serotonin uptake inhibition
St John's wort[b][50]	M/64y	Depression	Sertraline 75 mg/d[b]	None mentioned	Nausea, epigastric pain, anxiety	Synergistic serotonin uptake inhibition
St John's wort[50] 300mg bid for 2d	M/82y	Depression, status post left cerebrovascular accident	Sertraline 50 mg/d[b]	Aspirin and multivitamins	Nausea, vomiting, anxiety, confusion	Synergistic serotonin uptake inhibition

Contd over page

© Adis International Limited. All rights reserved.

Table I. Contd

Herbal medicine dosage/duration	Sex (M/F)/age	Diagnosis	Prescribed drug dosage/duration	Concomitant drugs	Clinical result of interaction	Possible mechanism
St John's wort[50] 300mg tid for 2d	M/79y	Depression and type 1 diabetes mellitus	Sertraline 50 mg/d[b]	Insulin	Nausea, anxiety, feelings of restlessness and irritability	Synergistic serotonin uptake inhibition
St John's wort[51] dosage unclear; for 5 wks	M/28y	Depression	Sertraline 50 mg/d for 5 wks	Testosterone (after post-orchidectomy)	Manic episode	Synergistic serotonin uptake inhibition
St John's wort[52] 600 mg/day for 10d	F/50y	Asthma and depression	Paroxetine 40 mg/d for 8mo. Replacing paroxetine with St John's wort for 10d. After this period, an acute dose of 20mg	No other tranquilisers	Nausea, weakness, fatigue, groggy and lethargic state.	Synergistic serotonin uptake inhibition
St John's wort[53] (0.3% hypericin) 300 mg/d for 2mo	F/42y White	None reported	Theophylline 300mg bid for several months followed by 1 dose of 80mg bid	Furosemide, potassium, morphine, zolpidem, valproic acid, ibuprofen, amitriptyline, salbutamol (albuterol), prednisone, zafirlukast, triamcinolone	Decreased theophylline levels	Hepatic enzyme induction
St John's wort[b][42]	F/75y	Polymorbid	Phenprocoumon[b]	None mentioned	Increased 'Quick-Wert' test (indicating decreased anticoagulant effect)	Hepatic enzyme induction
St John's wort[b][49]	F/79y	None reported	Warfarin 2.5y[b]	None mentioned	Decreased INR (from 2.5-3.8 to 1.7)	Hepatic enzyme induction
St John's wort[b][49]	M/65y	None reported	Warfarin 4y[b]	None mentioned	Decreased INR (from 2.4-3.6 to 2.0-2.1	Hepatic enzyme induction
St John's wort[b][49]	M/76y	None reported	Warfarin 10d[b]	None mentioned	Decreased INR (from 2.6 to 1.1)	Hepatic enzyme induction
St John's wort[b][49]	F/61y	None reported	Warfarin many years[b]	None mentioned	Decreased INR (INR before treatment not available; INR after 1.2)	Hepatic enzyme induction
St John's wort[b][49]	F/84y	None reported	Warfarin more than 6mo[b]	None mentioned	Decreased INR (from 2.9-3.6 to 1.5)	Hepatic enzyme induction
St John's wort[b][49]	F/56y	None reported	Warfarin[b]	None mentioned	Decreased INR (from 2.6 to 1.5)	Hepatic enzyme induction
St John's wort[b][49]	F/85y	None reported	Warfarin long-term[b]	None mentioned	Decreased INR (from 2.1-4.1 to 1.5)	Hepatic enzyme induction

a Sex (and/or age) not reported.

b Dose (and/or duration of the treatment) not reported.

c Use of trade name is for identification purposes only, and does not imply endorsement.

bid = twice daily; **cAMP** = cyclic adenosine triphosphate; **GABA** = γ-aminobutyric acid; **INR** = international normalised ratio; **LI160** = hypericum extract standardised to 0.3% hypericin; **MAO** = monoamine oxidase; **tid** = three times daily.

© Adis International Limited. All rights reserved.

life.[55] The latter study demonstrated that ginkgo has no effect on the hepatic microsomal drug oxidation system.

2.3 Ginseng

Ginseng (*Panax ginseng*) is marketed for a wide range of indications with tentative evidence in support of its efficacy.[78] Case reports of suspected interactions with warfarin[39] and the monoamine oxidase inhibitor (MAOI) phenelzine[37,38] have been reported. In the former case,[39] a decrease of INR was noted but because the patient took several other drugs concomitantly, causality is uncertain. In the latter cases,[37,38] the patients experienced insomnia, headache, tremulousness and mania; causality is likely because inadvertent rechallenge resulted in similar symptoms.[37] Three years later, one of these patients again ingested ginseng capsules (2 capsules for three days). She again experienced sleeplessness, tremors and headaches, but in contrast to her previous experience she became significantly more depressed, despite taking phenelzine 45 mg/day.[79] Ginsenosides, one active ingredient of ginseng, inhibits cyclic adenosine monophosphate (cAMP) phosphodiesterase and thus increase cAMP levels.[80] This effect may account partly for its psychoactive central effect both alone or in combination with MAOIs. However, the exact mechanism requires further study.

Ginseng decreased plasma alcohol concentrations in mice by delaying gastric emptying with ginsenosides being responsible for this phenomenon.[81,82] The effect could explain the ginseng-induced enhancement of blood alcohol clearance noted in one clinical study.[57] The authors also hypothesise that the effect could be due to induction of the essential components of the microsomal alcohol oxidising system, CYP system and nicotinamide adenine dinucleotide phosphate (NADPH)-cytochrome c reductase.[57]

Interactions of ginseng with influenza vaccine have been mentioned in one report, albeit without sufficient details.[10] A clinical trial[58] reported no negative effects on 24 safety parameters in volunteers taking ginseng in combination with anti-influenza polyvalent vaccine. However, eight adverse events (mainly insomnia and nausea) were reported in the ginseng plus influenza vaccine group.

2.4 Kava

Kava (*Piper methysticum*) is an effective herbal anxiolytic.[27] An interaction with alprazolam apparently caused a semicomatose state in one patient.[40] Kava might have additive effects with benzodiazepines; both act on the same receptors and on the same areas of the CNS with increased GABA receptors.[83]

Kava possesses dopamine antagonistic properties,[84] and cases of patients developing clinical signs suggestive of central dopaminergic antagonism have been described.[41] The dopamine antagonistic properties of kava could explain the increase in the duration and number of 'off' periods in a patient with Parkinson's treated concomitantly with levodopa.[41]

The hypnotic action of both alcohol and kava has been shown to increase when administered in combination to mice.[85] It is generally recommended not to take kava in conjunction with alcohol.[85] However, one clinical study showed that kava did not influence safety-related performances in volunteers taking alcohol.[59]

2.5 St. John's Wort

St John's wort (*Hypericum perforatum*) is effective for mild to moderate depression.[86-88] As a monotherapy, St John's wort has a most encouraging safety profile.[89] However, numerous reports indicate the possibility of important interactions, particularly with drugs metabolised by the CYP monoxygenase enzyme system and with selective serotonin-reuptake inhibitors (SSRIs).

The enzyme-inducing properties of St John's wort were investigated in five trials[66-70] using either internal (6β-hydroxycortisol/cortisol ratio)[66,67] or external probe substrates (dextromethorphan, alprazolam, caffeine).[68-70] Although an experimental study *in vitro*[90] and a clinical study did not yield the same results,[70] four clinical studies[66-69]

© Adis International Limited. All rights reserved.

Table II. Clinical trials in human volunteers of interactions between herbal medicines and drugs

Herbal medicine dosage/duration	Comedication dosage/duration	Study design	Sample size and description	Clinical result of interaction	Possible mechanism
Garlic[54] daily doses of aged garlic extract for 3mo (equivalent to 6-7 cloves of garlic daily)	Paracetamol (acetaminophen)[a]	Before-after comparison	16 M (25.75 ± 3.96y)	Changes in pharmacokinetic variables[d]	Not known
Ginkgo[55] 400 mg/d for 13 days	Phenazone (antipyrine) 10 mg/kg before and after ginkgo (day 14)	Randomised, placebo-controlled 3-way (phenytoin group served as a positive control)	25 M (15-35y)	Ginkgo (in contrast to phenytoin) does not affect antipyrine half-life	Not applicable
Ginkgo[56] 80mg tid for 8 wks	LHRH and TRH[b] (stimulation test) after 4 and 8 wks	Nonblind, before-after comparison	7 M (20-35y)	No changes in basal FSH, LH, prolactin and TSH levels	Not applicable
Ginseng[57] (water extract yielding 50% of the dry weight of the root); 3g/65kg single dose	Alcohol 72g/65kg single dose along with ginseng	Before-after comparison, (1 week washout period)	14 M (25-35y)	Lowering of blood alcohol concentrations (32.5%)	Delayed gastric emptying by ginsenosides
Ginseng[58] (Ginsana® G115)[e] 100 mg/day for 12 wks	Influenza vaccine (Agrippal® 0.05 ml)[e] administered at wk 4 during ginseng treatment	Randomised, placebo-controlled, double-blind with 2 parallel groups	132 M and 95 F [114 ginseng (mean age 48y), 113 placebo (mean age 48.5y)], sex not reported	No significant differences in 24 safety parameters[e]	Not applicable
Kava[59] (kava extract WS1490) 100mg tid for 8d	Alcohol at individual dose to achieve a 0.05% blood concentration at days 1, 4 and 8 (concomitantly with kava)	Randomised, placebo-controlled, double-blind with parallel groups	10 M, 10 F (18-60y)	No effect on safety-related performances	Not applicable
St John's wort[60] (LI 160) 300mg tid for 7d	Alcohol at individual dose to achieve a 0.45-0.8 mg/ml blood concentration at day 7 (concomitantly with St John's wort)	Randomised, placebo-controlled, double-blind, crossover	16 M, 16 F (25-40y)	No changes in cognitive capacities	Not applicable
St John's wort[61] (Aristofora®)[e] 3 capsules daily for 9d; last day 6 capsules along with alcohol (each capsule containing 0.25mg hypericin)	Alcohol at individual doses to achieve a 0.05% blood concentration at day 15 (concomitantly with St John's wort)	Placebo-controlled, 3-way, crossover (one group received a mixture of valerian and St John's wort)	6 M, 12 F (mean age 45.6 ± 11.2)	St John's Wort did not decrease alcohol-induced changes in vigilance (either alone or in combination with valerian)	Not applicable
St John's wort[62] (LI 160) 900 mg/day for 14d	Amitriptyline 75mg bid for 14d along with St John's wort	Nonblind	12 pts with depression (age and sex not reported)	Decreased plasma amitriptyline concentrations (21.7%) and of its metabolite nortriptyline (40.6%)	Induction of hepatic enzymes
St John's wort[63] (LI 160) 300mg tid for 10d	Digoxin for 15d; days 1-4 administered alone; days 5-15 with St John's wort	Single blind, placebo-controlled with parallel groups	13 M, 12 F (12 placebo and 13 treated) [22-32y]	Decreased plasma digoxin concentration - trough concentration (33.3%), AUC (25%) and C_{max} (26%)	Induction of the intestinal P-glycoprotein

© Adis International Limited. All rights reserved.

St John's wort[64] (preparation standardised to 0.3% hypericin) 300mg tid for 16d	Indinavir: after achieving the steady state, single 800mg dose (before and after St John's wort treatment)	Nonblind, before-after comparison	6 M, 2 F (29-50y)	AUC of indinavir decreased 57%	Hepatic enzyme induction
St John's Wort[65] (LI 160) 300 mg/day for 11d	Phenprocoumon 12mg, single dose before and after St John's wort or placebo (day 11)	Randomized, single blind, placebo-controlled, cross-over (2-week washout period)	10 healthy M (18-50y)	AUC of free phenprocoumon decreased 17.4%	Hepatic enzyme induction
St John's Wort[66] 300mg tid for 2 wks	6β-Hydroxycortisol, D-glucaric acid and cortisol[c]	Before-after comparison	27 M, 23 F (21-35y)	Urinary excretion of 6β-hydroxycortisol increased 41%; no changes in urinary excretion of cortisol	Hepatic enzyme induction
St John's wort[67] (standardised to 0.3% hypericin) 300mg tid for 14d	6β-Hydroxycortisol/cortisol ratio[c]	Nonblind, before-after comparison	4 M, 9 F (18-45y)	Urinary excretion of 6β-hydroxycortisol/cortisol ratio increased (114%)	Hepatic enzyme induction
St John's wort[68] (Solaray®[e], standardised to 0.3% hypericin) 300mg tid for 3d	Alprazolam 1mg in 3 or 2mg in 4 and dextromethorphan 30mg before and after St John's wort (day 3)	Before-after comparison	4 M, 3 F (24-32y)	AUC of alprazolam 2mg decreased 48%	Hepatic enzyme induction
St John's wort[69] 300mg tid for 8d	Dextromethorphan 30mg before and after St John's wort (day 8)	Before-after comparison	16 (sex and age not reported)	Trend to increase the metabolism of dextromethorphan	Hepatic enzyme induction
St John's wort[70] 300mg tid for 8d	Caffeine 200mg before and after St John's wort (day 8)	Before-after comparison	16 (sex and age not reported)	No changes in plasma and urine caffeine metabolite concentrations	Not applicable

a One gram of paracetamol (acetaminophen) was administered to each participant on five separate occasions: immediately before garlic; at the end of the first, second and third month of garlic; and finally at 1 month after cessation of garlic.

b Dose not reported.

c Basal physiological levels were measured.

d Increase in peak plasma paracetamol (acetaminophen) concentration of after 1 month garlic, increase in plasma paracetamol (acetaminophen) concentrations and decreased paracetamol (acetaminophen) renal clearance after 2 months' treatment; increased in plasma acetaminophen glucuronide concentrations after 3 months' garlic; increase in peak plasma acetaminophen sulphate concentration 1 month after garlic administration had ended.

e Use of trade name is for identification purposes, and does not imply endorsement.

f Erythrocyte sedimentation rate, haemoglobin, haematocrit, leucocytes, neutrophils, basophils, eosinophils, lymphocytes, monocytes, red blood cell count, albumin, glucose, blood urea nitrogen, creatinine, total protein, alkaline phosphatase, total bilirubin, aspartate amino transferase, alanine amino transferase, γ-glutamyl transpeptidase, lactic dehydrogenase, sodium, potassium, chloride.

AUC = area under the plasma concentration/time curve; **bid** = twice daily; $\mathbf{C_{max}}$ = maximum plasma concentration; **FSH** = follicle stimulant hormone; **LI160** = hypericum extract standardised to 0.3% hypericin; **LHRH** = luteinising hormone releasing hormone; **tid** = three times daily; **TRH** = thyrotropin releasing hormone; **TSH** = thyroid-stimulating hormone; **LH** = luteinising hormone.

© Adis International Limited. All rights reserved.

showed an increase or a trend to increase the metabolic capacity of CYP enzymes.

In addition to the enzyme-inducing properties of St John's wort, other evidence indicates that flavonoids contained in St John's wort raise the activity of P-glycoprotein,[91] which, in turn, increases the elimination of drugs. Probably via these mechanisms it has been shown to reduce the plasma concentrations of warfarin,[49] phenprocoumon,[42,65] oral contraceptives,[42,49] cyclosporin,[42-47] amitriptyline,[62] theophylline,[53] and the protease inhibitor indinavir.[64] Plasma digoxin concentrations[63] are also likely to be decreased through an induction of P-glycoprotein, as oxidative hepatic metabolism plays only a minor role in the elimination of digoxin.[92]

When given in parallel with other SSRIs (sertraline, paroxetine) or serotonin nonadrenaline reuptake inhibitors (nefazodone), St John's wort can cause symptoms of central serotonin excess as suggested by seven case reports.[50-52] These effects could be the result of an additive effect on serotonin reuptake, as hyperforin in St John's wort inhibits serotonin reuptake.[93,94] The symptoms of central serotonergic syndrome include mental status changes, tremor, autonomic instability, gastrointestinal upsets, headache, myalgias, and motor restlessness.[95] The syndrome can be serious, even fatal, particularly in the elderly. The serotonin receptor antagonist cyproheptadine is potentially useful in reversing some of these symptoms.

A brief episode of acute delirium, possibly induced by exposure to St John's wort, valerian and loperamide has also been described.[48] These symptoms could be a MAOI-induced reaction to a drug or food product, an interaction between St John's wort and valerian, or an interaction of these herbal medicines with loperamide, which could theoretically induce a MAOI-drug reaction. A report has suggested that loperamide alone can cause delirium, although causality is unproven.[96]

Finally, two clinical trials[60,61] have suggested that St John's wort did not change cognitive capacities[60] or safety-related parameters (visual orientation, forced concentration, acoustic reaction time, choice reaction time, stress tolerance, vigilance and motor co-ordination) following co-administration with alcohol.[61]

Given the widespread use of St John's wort, the implications of the emerging evidence of interactions are serious. In many countries such as the US, UK and Sweden, extracts of St John's wort are marketed as food supplements.[97] Patients often self-medicate St John's wort in the belief that herbal treatments are by definition free of risks.

2.6 Echinacea

Echinacea (*Echinacea augustifolia, Echinacea pallida, Echinacea purpurea*) is used for stimulating the immune system. The clinical evidence in support is promising but not fully conclusive.[98] Theoretically, echinacea extracts might decrease the effects of immunosuppressants.[10,17] However, no clinical cases of drug interactions have been reported.

2.7 Saw Palmetto

Saw palmetto (*Serenoa repens*) is an effective symptomatic short-term treatment for benign prostate hyperplasia, possibly through hormonal effects.[99] Therefore, it could interact with concomitant hormone therapies[10,17] but no clinical evidence exists for this theoretical possibility. There are no suggestions of interactions with any other medication.

3. Limitations

The data presented in section 2 also have obvious limitations. For many of the interactions listed, our understanding of the mechanisms involved is incomplete (tables I and II). Much of the literature on herbal medicine is limited by the fact that the authors of clinical reports fail to adequately define the botanicals used.[100] All pharmacologically active herbal extracts are associated with varying degrees of toxicity in their own right.[101] Often case reports do not allow a clear distinction between adverse events due to toxicity and those caused by herb-drug interactions. These limitations amount

© Adis International Limited. All rights reserved.

to a significant challenge for further research in this area.

4. Conclusion

Herb-drug reactions are a reality and can present a serious threat to human health. Healthcare professionals should be aware of this potential and researchers should strive to fill the numerous gaps in our present understanding of this problem.

Acknowledgements

The authors wish to thank Dr Max Pittler and Clare Stevinson (both from the Department of Complementary Medicine, University of Exeter, UK) for their help.

References

1. Blumenthal M. Herb market levels after five years of boom. HerbalGram 1999; 47: 64-5
2. Gruenwald J. The supplement markets in the US and Europe. Neutraceuticals World 2000 Jul/Aug: 36-7
3. Ernst E. Herbal medicine. A concise overview for professionals. Oxford: Butterworth Heinemann, 2000
4. Ernst E. Herbal medicines: where is the evidence? BMJ 2000; 321: 395-6
5. Ernst E. Harmless herbs? A review of the recent literature. Am J Med 1998; 104: 170-8
6. Fugh-Berman A. Herb-drug interactions. Lancet 2000; 355: 134-8
7. Eisenberg D, David RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997. JAMA 1998; 280: 1569-75
8. Hobbs WR, Rall TW, Verdoorn TA. Hypnotics and sedatives: ethanol. In: Hardman JG, Goodman Gilman A, Molinoff PB, et al. editors. Goodman & Gilman's The pharmacological basis of therapeutics. 9th ed. New York (NY): McGraw Hill, 1996: 361-96
9. Brinker F. Herb contraindications and drug interactions. Sandy (OR): Eclectic Medical Publications, 1998
10. Lininger SW. A-Z guide to drug-herb-vitamin interactions. Rocklin (CA): Prima Publishing, 1999
11. Meletis CD, Jacobs T. Interactions between drugs and natural medicines. Sandy (OR): Eclectic Medical Publications, 1999
12. Cupp MJ. Herbal remedies: adverse effects and drug interactions. Am Fam Physician 1999; 59: 1239-45
13. Klepser TB, Klepser ME. Unsafe and potentially safe herbal therapies. Am J Health Syst Pharm 1999; 56: 125-37
14. Barrett B, Kiefer D, Rabago D. Assessing the risks and benefits of herbal medicine: an overview of scientific evidence. Altern Ther 1999; 5: 40-9
15. Smolinske, SC. Dietary supplement-drug interactions. J Am Med Womens Assoc 1999; 4: 191-2
16. Miller LG. Herbal medicinals. Selected clinical considerations focusing on known or potential drug-herb interactions. Arch Intern Med 1998; 158: 2200-11
17. Ernst E. Possible interactions between synthetic and herbal medicinal products. Part 1: a systematic review of the indirect evidence. Perfusion 2000; 13: 4-15
18. Leak JA. Perioperative considerations in the management of the patient taking herbal medicines. Curr Opin Anaesthesiol 2000; 13: 321-5
19. WHO monographs on selected medicinal plants. Vol. 1. Geneva: World Health Organisation, 1999
20. Boon H, Smith M. The botanical pharmacy. Kingston (ON): Quarry Press Kingston, 1999
21. Ross IA. Medicinal plants of the World. Totowa (NJ): Human Press, 1999
22. Cupp MJ. Toxicology and clinical pharmacology of herbal products. Totowa (NJ): Human Press, 2000
23. Foster S, Tyler VE. Tyler's honest herbal. New York (NY): The Haworth Herbal Press, 1999
24. Jepson RG, Kleijnen J, Leng GC. Garlic for peripheral arterial occlusive disease. Update software, CD000095. Oxford: The Cochrane Library, 2000
25. Diamond BJ, Shifflett SC, Feiwel N, et al. Ginkgo biloba extract: mechanisms and clinical indications. Arch Phys Med Rehabil 2000; 81: 668-78
26. Bahrke MS, Morgan WP. Evaluation of the erogogenic properties of ginseng. Sports Med 2000; 29: 113-33
27. Pittler MH, Ernst E. Efficacy of kava extract for treating anxiety: systematic review and meta-analysis. J Clin Psychopharmacol 2000; 20: 84-9
28. McIntyre M. A review of the benefits, adverse events, drug interactions, and safety of St John's wort (*Hypericum perforatum*): the implications with regard to the regulation of herbal medicines. J Altern Med 2000; 6: 115-24
29. Percival SS. Use of echinacea in medicine. Biochem Pharmacol 2000; 60: 155-8
30. Wilt T, Ishani A, Stark G, et al. Serenoa repens for benign prostatic hyperplasia. Update software, CD001423 Issue 2. Oxford: The Cochrane Library, 2000
31. Aslam M, Stockley I. Interaction between curry ingredient (karela) and drug (chlorpropamide). Lancet 1979; I: 607
32. Sunter WH. Warfarin and garlic. Pharm J 1991; 246: 772
33. Rosenblatt M, Mindel J. Spontaneous hyphema associated with ingestion of Ginkgo biloba extract. N Engl J Med 1997; 336: 1108
34. Shaw D, Leon D, Kolev S, et al. Traditional remedies and food supplements: a 5-year toxicological study (1991-1995). Drug Saf 1997; 17: 342-56
35. Galluzzi S, Zanetti O, Binetti G, et al. Coma in a patient with Alzheimer's disease taking low dose trazodone and ginkgo biloba. J Neurol Neurosurg Psychiatry 2000; 68: 679-83
36. Matthews MK. Association of Ginkgo biloba with intracerebral haemorrhage. Neurology 1998; 5: 1933
37. Shader RI, Greenblatt DJ. Phenelzine and the dream machine – ramblings and reflections. J Clin Psychopharmacol 1985; 5: 65
38. Jones BD, Runikis AM. Interaction of ginseng with phenelzine. J Clin Psychopharmacol 1987; 7: 201-2
39. Janetzky K, Morreale AP. Probable interactions between warfarin and ginseng. Am J Health Syst Pharm 1997; 54: 692-3
40. Almeida JC, Grimsley EW. Coma from the health food store: interaction between kava and alprazolam. Ann Intern Med 1996; 125: 940-1
41. Scheloscky L, Raffauf C, Kendroska K, et al. Kava and dopamine antagonism. J Neurol Neurosurg Psychiatry 1995; 58: 639-40
42. Bon S, Hartmann K, Kubn M. Johanniskraut: Ein Enzyminduktor? Schweitzer Apothekerzeitung 1999; 16: 535-6
43. Breidenbach Th, Kliem V, Burg M, et al. Profound drop of cyclosporin. A whole blood trough levels caused by St John's

© Adis International Limited. All rights reserved.

Wort (*Hypericum perforatum*). Transplantation 2000; 69: 2229-32
44. Breidenbach Y, Hoffmann MW, Becher T, et al. Drug interaction of St John's wort with cyclosporin. Lancet 2000; 355: 1912
45. Roots I, Johne A, Maurer A, et al. Arzneimittel interaktionen von hypericum-extract. Proc Germ Soc Pharmacol 2000 Jun 16-17; Berlin
46. Rey JM, Walter G. *Hypericum perforatum* (St John's wort) in depression: pest or blessing? Med J Aust 1998; 169: 583-6
47. Ruschitzka F, Meier PJ, Turina M, et al. Acute heart transplant refection due to Saint John's wort. Lancet 2000; 355: 548-9
48. Khawaja IS, Marotta RF, Lippmann S. Herbal medicines as a factor in delirium. Psychiatric services 1999; 50: 969-70
49. Yue Q-Y, Bergquist C, Gerden B. Safety of St John's wort (*Hypericum perforatum*). Lancet 2000; 355: 576-7
50. Lantz MS, Buchalter E, Giambanco V. St. John's wort and antidepressant drug interactions in the elderly. J Geriatr Psychiatry Neurol 1999; 12: 7-10
51. Barbenel DM, Yusufi B, O'Shea D, et al. Mania in a patient receiving testosterone replacement post-orchidectomy taking St John's wort and sertraline. J Psychopharmacol 2000; 14: 84-6
52. Gordon JB. SSRIs and St. John's wort: possible toxicity? Am Fam Phys 1998; 57: 950
53. Nebel A, Schneider BJ, Baker RK, et al. Potential metabolic interaction between St. John's wort and theophylline. Ann Pharmacother 1999; 33: 502
54. Gwilt PR, Lear CL, Tempero MA, et al. The effect of garlic extract on hyman metabolism of acetaminophen. Cancer Epidemiol, Biomarkers Prev 1994; 3: 155-60
55. Duche JC, Barre J, Guinot P, et al. Effect of ginkgo biloba extract on microsomal enzyme induction. Int J Clin Pharmacol Res 1998; 9: 165-8
56. Felber JP. Effet de l'extrait de ginkgo biloba sur le parametres biologiques endocriniens. Presse Med 1986; 15: 1573-4
57. Lee FC, Ko JH, Park JK, et al. Effects of panax ginseng on blood alcohol clearance in man. Clin Exp Pharmacol Physiol 1987; 14: 543-6
58. Scaglione F, Cattaneo G, Alessandria M, et al. Efficacy and safety of the standardised ginseng extract G115 for potentiating vaccination against the influenza syndrome and protection against the common cold. Drugs Exp Clin Res 1996; 22: 65-72
59. Herberg WK. Zum Einfluss von Kava-spezialextrakt WS1490 in kombination mit ethylalkohol auf sicherheitsrelevante leistungsparameter. Blutalkohol 1993; 30: 96-105
60. Schmidt U, Harrer G, Kuhn U, et al. Wechselwirkungen von hypericum-xtrakt mit alkohol. Neuenheilkunde 1995; 12: 314-9
61. Herberg KW. Alternative zu synthetischen Psychopharmaka? Therapiewoche 1994; 44: 704-13
62. Roots I, Johne A, Schmider I, et al. Interaction of a herbal extract from St John's wort with amitriptyline and its metabolites. Clin Pharmacol Ther 2000; 67: 159
63. Johne A, Brockmoller J, Bauer S, et al. Pharmacokinetic interaction of digoxin with an herbal extract from St John's wort (*Hypericum perforatum*). Clin Pharmacol Ther 1999; 66: 338-45
64. Piscitelli SC, Burstein AH, Chaitt D, et al. Indinavir concentrations and St John's wort. Lancet 2000; 355: 547-8
65. Donath F, Roots I, Langheinrich M, et al. Interaction of St John's wort extract with phenprocoumon. Eur J Clin Pharmacol 1999; 55: A22
66. Kerb R, Bauser J, Brockmoller J, et al. Urinary 6 β-hydroxycortisol extretion rate is affected by treatment with hypericum extract [abstract]. Eur J Clin Pharmacol 1997; 52: A186
67. Roby CA, Anderson GD, Kantor E, et al. St John's wort: effect on CYP3A4 activity. Clin Pharmacol Ther 2000; 67: 451-7
68. Markowitz JS, DeVane CL, Boulton DW, et al. Effect of St John's wort (*Hypericum perforatum*) on cytochrome P-450 2D6 and 3A4 activity in healthy volunteers. Life Sci 2000; 66: PL133-9
69. Ereshefsky B, Gewertz N, Francis Lam YW, et al. Determination of SJW differential metabolism at CYP2D6 and CYP3A4, using dextromethorphan probe methodology. Proceedings of the 39th Meeting of the NCDEU; 2000 Jul 20-21; Boca Raton (FL): P130
70. Gewertz N, Ereshefsky B, Francis Lam YW, et al. Determination of the differential effects of St John's wort on the CYP1A2 and NAT2 metabolic pathways using caffeine probe methodology. Proceedings of the 39th Meeting of the NCDEU; 2000 Jul 20-21; Boca Raton (FL): P131
71. Burnham BE. Garlic as a possible risk for postoperative bleeding. Plast Reconstruc Surg 1995; 95: 213
72. German K, Kumar U, Blackford HN. Garlic and the risk of TURP bleeding. Br J Urol 1996; 76: 518
73. Zacharias NT, Sebastian KL, Philip B, et al. Hypoglycemic and hypolipidaemic effects of garlic in sucrose fed rabbits. Indian J Physiol Pharmacol 1980; 24: 151-4
74. Sitprija S, Plengvidhya C, Kangkaya V, et al. Garlic and diabetes mellitus phase II clinical trials. J Med Assoc Thai 1987; 70 Suppl. 2: 223-7
75. Rowin J, Lewis SL. Spontaneous bilateral subdural hematomas associated with chronic ginkgo biloba ingestion. Neurology 1996; 46: 1775-6
76. Medina JH, Viola H, Wolfman C, et al. Overview-flavonoids: a new family of benzodiazepine receptor ligands. Neurochem Res 1997; 22: 419-25
77. Koley AP, Buters JTM, Robinson RC, et al. Differential mechanisms of cytochrome P45O inhibition and activation by α-naphthoflavone. J Biol Chem 1997; 272: 3149-52
78. Vogler BK, Pittler MH, Ernst E. The efficacy of ginseng. A systematic review of randomised clinical trials. Eur J Clin Pharmacol 1999; 55: 567-75
79. Shader RI, Greenblatt D. Bees, ginseng and MAOs revisited. J Clin Psychoparmacol 1988; 8: 235
80. Stancheva SL, Alova LG. Ginsenoside Rg1 inhibits the brain cAMP phosphodiesterase activity in young and aged rats. Gen Pharmacol 1993; 24: 1459-62
81. Lee YJ, Pantuck CB, Pantuck EJ. Effect of ginseng on plasma levels of ethanol in the rat. Planta Medica 1993; 59: 17-9
82. Koo MW. Effects of ginseng on ethanol induced sedation in mice. Life Sci 1999; 64: 153-60
83. Jussofie A, Schmiz A, Hiemke C. Kavapyrone enriched extract from Piper methysticum as a modulator of GABA binding sites in different regions of rat brain. Psychopharmacology Berl 1994; 116: 469-74
84. Jamieson DD, Duffield PH, Cheng D, et al. Comparison of the central nervous system activity of the aqueous and lipid extract of kava (Piper methysticum). Arch Int Pharmacodyn Ther 1989; 301: 66-80
85. Jamieson DD, Duffield PH. Positive interaction of ethanol and kava resin in mice. Clin Exp Pharmacol Physiol 1990; 17: 509-14
86. Linde K, Ramirez G, Mulrow CD, et al. St John's wort for depression – an overview and meta-analysis of randomised clinical trials. BMJ 1996; 313: 253-8

© Adis International Limited. All rights reserved.

87. Linde K, Mulrow CD. St John's wort for depression (Cochrane Review). Update software. Issue 3. Oxford: The Cochrane Library, 2000
88. Gaster B, Holroyd J. St John's wort for depression: a systematic review. Arch Intern Med 2000; 160: 152-6
89. Stevinson C, Ernst E. Safety of Hypericum in patients with depression: a comparison with conventional antidepressants. CNS Drugs 1999; 11 (2): 125-32
90. Obach RS. Inhibition of huyman cytochrome P450 enzymes by constituents of St John's wort, an herbal preparation used in the treatment of depression. J Pharmacol Exp Ther 2000; 294: 88-95
91. Conseil G, Baubichon-Cortay H, Dayan G, et al. Flavonoids: a class of modulators with bifunctional interactions at vicinal ATP- and steroid-binding sites on mouse P-glycoprotein. Proc Natl Acad Sci USA 1998; 95: 9831-6
92. Lacarelle B, Rahmani R, de Sousa G, et al. Metabolism of digoxin, digixigenin digitoxosides and digoxigenin in human hepatocytes and liver microsomes. Fundam Clin Pharmacol 1991; 5: 567-82
93. Müller WE, Rolli M, Schafer C, et al. Effects of hypericum extract (LI160) in biochemical models of antidepressant activity. Pharmacopsychiatry 1997; 30 Suppl. 2: 102-7
94. Müller WE, Singer A, Wonnemann M, et al. Hyperforin represents the neurotransmitter reuptake inhibiting constituent of hypericum extract. Pharmacopsychiatry 1998; 31 Suppl. 1: 16-21
95. Brown TM, Skop BP, Mareth TR. Pathophysiology and management of the serotonin syndrome. Ann Pharmacother 1996; 30: 527-33
96. Schwartz RH, Rodrigues WJ. Toxic delirium possibly caused by loperamide. J Pediatrics 1991; 118: 656-7
97. Ernst E. Second thoughts about the safety of St John's wort. Lancet 1999; 354: 2014-6
98. Melchart D, Linde K, Fisher P, et al. Echinacea for the prevention and treatment of the common cold (Cochrane Review). Update software. Issue 1. Oxford: The Cochrane Library, 1999
99. Wilt TJ, Ishani A, Stark G, et al. Saw palmetto extracts for treatment of benign prostatic hyperplasia. JAMA 1998; 280: 1604-9
100. Tyler VE. Product definition deficiencies in clinical studies of herbal medicines. Scientific Rev Alt Med 2000; 4: 17-21
101. Ernst E, Eisenberg D, Pittler MH, et al. The desktop guide to complementary and alternative medicine. Edinburgh: Mosby, 2001

Correspondence and offprints: Dr *Edzard Ernst*, Department of Complementary Medicine, School of Postgraduate Medicine and Health Sciences, University of Exeter, 25 Victoria Park Road, Exeter EX2 4NT, United Kingdom.
E-mail: E.Ernst@exeter.ac.uk

© Adis International Limited. All rights reserved.